STUDY OF THE EFFECT OF THE CALCIUM CHANNEL BLOCKER VERAPAMIL ON THE HEALING OF HYPERTROPHIC SCARS AND KELOIDS

A dissertation submitted to Dr MGR Medical University, Chennai, in partial fulfillment of requirement for the degree of Doctor of Medicine in Pharmacology (Branch V1) Examination to be held in March 2007.

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CERTIFICATE

This is to certify that the dissertation entitled **"STUDY OF THE EFFECT OF THE CALCIUM CHANNEL BLOCKER VERAPAMIL ON THE HEALING OF HYPERTROPHIC SCARS AND KELOIDS"** is the bonafide original work of Dr.Margaret Shanth toward the MD- Branch V1 (Pharmacology) Degree, Examination of the Dr.MGR Medical University, Chennai, to be conducted in March 2007

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DECLARATION

I, Dr Margaret Shanthi, do hereby declare that this dissertation **" Study of the effect of the calcium channel blocker verapamil on the healing of hypertrophic scars and keloids"** has not been submitted by me for the award of degree, in part or whole, to any other university.

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CONTENTS

LIST OF TABLES

CENTIMETER SCALE

CENTIMETER SCALE

LIST OF FIGURES

INTRODUCTION

Hypertrophic scars and keloids are dermal fibroproliferative disorders unique to humans that occur following trauma, inflammation, surgery, and that sometimes occur spontaneously (Meenakshi et al.,2005). They are characterized by an excess development of collagen in the dermis and subcutaneous tissues. Unlike the scar characteristics of normal wound repair, the exuberant scarring of keloid and hypertrophic scars results typically in disfigurement, contractures, pruritis and pain. Keloids occur in individuals with a familial disposition among Blacks, Hispanics and Orientals.

Hypertrophic scars develop within the boundary of the original scar and may spontaneously regress over time, whereas keloids extend beyond the wound boundary and tend to remain elevated. Other differences between hypertrophic and keloid scars include histologic, morphologic and cellular response to growth factors, and scar appearance. These cutaneous fibrotic conditions can be caused by minor trauma to the skin, such as ear piercing, abrasion, tattooing and burns (English and Shenefelt, 1999).

Clinically hypertrophic scars and keloids are characterized by excessive dermal fibrosis and scarring resulting from an imbalance in collagen synthesis and degradation during wound healing. Control of hypertrophic scars and keloids is a difficult challenge in surgical practice (Rockwel et al., 1989***).*** Scars can cause functional and aesthetic problems during the operative and postoperative healing periods of burn victims. More recently, abnormal interaction between epidermal

parenchymal cells and regulatory genes such as TP53 has been suggested to be involved in the pathogenesis of hypertrophic scars and keloids (Teofoli et al., 1999). Scars occur more commonly in dark skinned individuals. Wounds that cross skin tension lines, wounds located on the ear lobes, on the sternum or deltoid areas commonly show tendency for scarring.

Currently there are several accepted approaches for the reduction of hypertrophic scars and keloids. Each treatment has its various advantages and disadvantages in terms of efficacy, convenience and cost. The most common therapeutic approach is application of compression bandages for at least 6 to 12months (Davie, 1985). Although application of silicon gel sheet is effective in reducing hypertrophic scars and keloids (Fulton,1995) its application on certain anatomical locations is difficult. Collagen, and mucopolysccharide creams (Magliaro et al., 1999), radiotherapy (Klumpar et al., 1994***),*** laser therapy (Connell and Harland 2000), interferon therapy (Berman and Flores, 1997), bleomycin (Farahnaz et al, 2005*)* and intralesional corticosteroids have been the cornerstone of treatment and prophylaxis of hypertrophic scars and keloids (Darzi et al.,1992). The most commonly used corticosteroid is tramicinolone acetonide (TAC) at a concentration of 40mg/ml, 1ml of which is administered intralesionally. Corticosteroids act by suppressing inflammatory cell migration, and inhibition of fibroblast proliferation at high doses. Systemic absorption of corticosteroids may cause adrenal suppression. Local adverse effects include skin atrophy, telengiectasis, depigmentation and ulceration. Scar recurrence after stopping corticosteroid treatment is relatively common.

This study was been conducted to assess the efficacy of verapamil and triamcinolone in keloids and hypertrophic scars with regard to appearances, symptomatic improvement, patient satisfaction and complications. Verapamil has been shown to stimulate procollagenase synthesis in keloid, hypertrophic and normal human cultured fibroblasts, resulting in depolymerization of actin filaments, alteration of their cell shape, and reduction of the fibrous tissue production (Doong et al., 1996).

AIM

To determine whether the calcium channel blocker verapamil has the potential to be used for the treatment of keloids and hypertrophic scars in the future.

OBJECTIVES

- To evaluate the effects of Verapamil in the treatment of hypertrophic scars and keloids.
- To study the effect of verapamil on the rate of reduction of hypertrophic scars and keloids in comparison with triamcinolone.

REVIEW OF LITERATURE

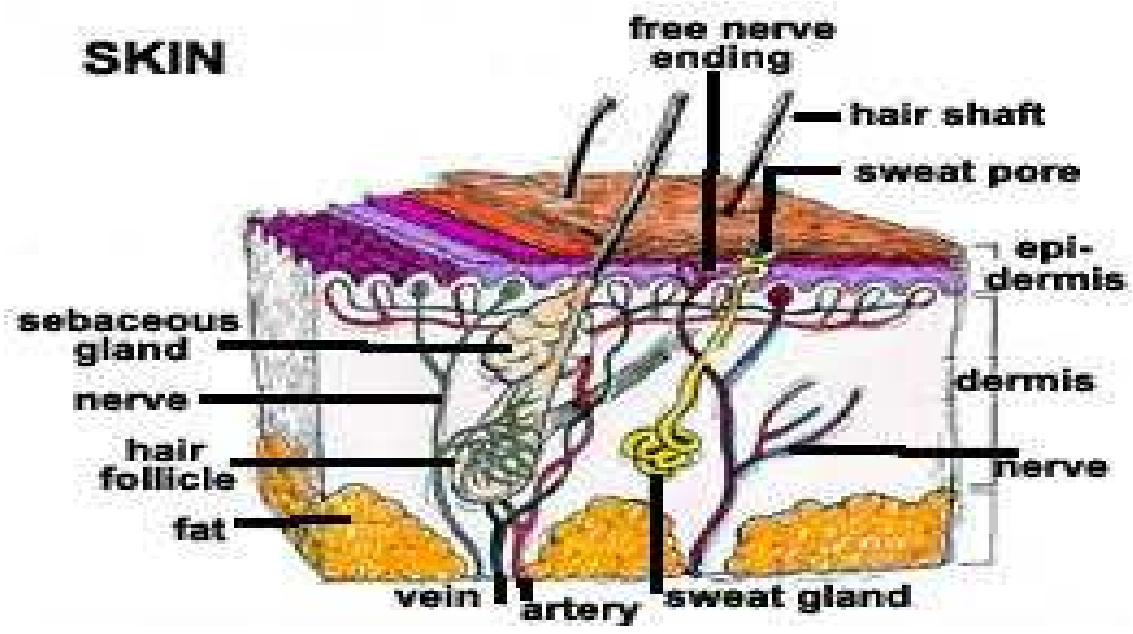
ANATOMY OF SKIN

The skin is an ever-changing organ that contains many specialized cells and structures. The skin functions as a protective barrier. It is also very much involved in maintaining the proper temperature for the body to function well. It gathers sensory information from the environment, and plays an active role in immunological protection from disease.

Structure of the skin:

The skin consists of the epidermis, dermis and subcutaneous tissue (Tortora and Grabowski.,1999).

Figure 1



EPIDERMIS

The epidermis is the outer layer of skin. The thickness of the epidermis varies in different types of skin. It is the thinnest on the eyelids at 0.05 mm and the thickest on the palm and soles at 1.5 mm. The epidermis contains 5 layers. From bottom to top the layers are named stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum. The bottom layer, the stratum basale, has cells that are shaped like columns. In this layer the cells divide and push already formed cells into higher layers. As the cells move into the higher layers, they flatten and eventually die. The top layer of the epidermis, the stratum corneum, is made of dead, flat skin cells that shed about every week. There are three types of specialized cells in the epidermis. The melanocyte produces the pigment melanin, the Langerhans' cell is the frontline defense of the immune system in the skin, and the Merkel's cell's function is unclear.

DERMIS

The dermis also varies in thickness depending on the location of the skin. It is 0.3 mm on the eyelid and 3.0 mm on the back. The dermis is composed of three types of tissues that are present throughout and not in layers. The types of tissue are collagen, elastic tissue, and reticular fibers.

The two layers of the dermis are the papillary and reticular layers. The upper, papillary layer contains a thin arrangement of collagen fibers. The lower

reticular layer is thicker and made of thick collagen fibers that are arranged parallel to the surface of the skin.

The dermis contains many specialized cells and structures. The hair follicles are situated here with the erector pili muscle that attaches to each follicle. Sebaceous (oil) glands and apocrine (scent) glands are associated with the follicle. This layer also contains sweat glands, but they are not associated with hair follicles. Blood vessels and nerves course through this layer. The nerves transmit sensations of pain, itch, and temperature. There are also specialized nerve cells called Meissner's and Vater-Pacini corpuscles that transmit sensations of touch and pressure.

SUBCUTANEOUS TISSUE

The subcutaneous tissue is a layer of fat and connective tissue that contains relatively large blood vessels and nerves. This layer is important for the regulation of temperature of the skin itself and the body. The size of this layer varies throughout the body and between individuals .

PHYSIOLOGY OF SKIN

The skin is the largest organ of the body. The skin and its derivatives (hair, nails, sweat and oil glands) make up the integumentary system of the body. One of the main functions of the skin is protection (Guyton and Hall, 2005). Skin serves several functions, which are introduced here:

Regulation of body Temperature : In response to high environmental temperature or strenuous exercise, the evaporation of sweat from the skin surface helps lower an elevated body temperature to normal.

Protection : The skin covers the body and provides a physical barrier that protects underlying tissues from physical abrasion, bacterial invasion, dehydration, and ultraviolet (UV) radiation.

Sensation : The skin contains abundant nerve endings and receptors that detect stimuli related to temperature, touch, pressure, and pain.

Excretion : Besides removing heat and some water from the body, sweat also is the vehicle for excretion of a small amount of salts and several organic compounds**.**

Immunity : Certain cells of the epidermis are important components of the immune system, which fends off foreign invaders.

Blood Reservoir : The dermis of the skin houses extensive networks of blood vessels that carry 8 to 10% of the total blood flow in a resting adult.

Synthesis of Vitamin D : Vitamin D is a group of closely related compounds. Synthesis of vitamin D begins with activation of a precursor molecule in the skin by ultraviolet (UV) rays in sunlight.

WOUND HEALING

When any trauma violates cutaneous integrity, a provisional wound matrix is created to fill the physical defect. Starting with the formation of a blood clot, inflammatory cells, proliferating endothelial cells, fibroblasts and endothelial cells move along the wound matrix. They form new blood vessels, continue production of provisional extra cellular matrix and migrate from the wound edges to create a layer that covers the surface of the open wound .In the newly created matrix skin collagen fibrils and elastin fibrils form a supporting frame work. This framework is saturated with a filler substance composed of proteoglycans and glycoprotein, which mediates the interaction between the wound matrix and the wound healing cells. Finally the amount of collagen and their fibril cross-linking increases to provides the scar's ultimate strength.

STAGES OF WOUND HEALING

Inflammatory stage occurs within hours of injury. Following the initial tissue injury, inflammatory mediators such as cytokines are released from the injured tissue cells and wound blood clot, which initiate the inflammatory stage. The amount of blood released, the extent of devitalized tissue and the bacterial content largely control the intensity of the inflammatory process (Weigus et al.,1981). The length of time before wound closure is a critical factor in wound inflammation.

Proliferative Stage occurs within days of injury. During the proliferative stage, the number and density of fibroblasts in the extracellular matrix increase. New blood vessels and epithelium are formed. The balance between tissue degradation and biosynthesis permits remodeling of the provisional tissue and also determines the net amount of scar tissue produced (McGrath, 1990).

Maturation stage occurs within months of injury. This stage is characterized by cellular apoptosis and a shift in balance from scar remodeling toward scar degradation .The process is accompanied by extracellular matrix reorganization and reduction. Metalloproteases synthesized during the proliferation stage continue to break down the extracellular matrix at a rate largely determined by physical and biochemical factors in the matrix (McCauley et al.,1992). The amount of extracellular matrix biosynthesis is controlled by need for tissue strength and other operational parameters. Mechanical stress is an important contributory parameter in net scar production.

In predisposed individuals, those wound healing processes show overabundant wound matrix responsible for raised, red and inflexible scar tissue which causes, itching, pain, functional limitation and cosmetic problems. At a certain unknown point a derailment of the protecting wound healing process occurs and excessive scar tissue formation will be initiated.

HISTOLOGY OF HYPERTROPHIC SCARS AND KELOIDS

Keloids and hypertrophic scars differ from normal skin and normal scars by their rich vasculature, high mesenchymal cell density, and thickened epidermal cell layer. Collagen fibers are organized in swirls. Cosman et al., (1961*)* made a thorough and exhaustive study of the epidemiology of keloids, and set up guidelines for the histological differentiation between hypertrophic scars and keloids. They suggested that the presence of broad eosinophilic refractile hyaline- like collagen fibers was the essential criterion for the diagnosis of keloids. Kischer and Brody *(*1981) suggested that the collagen nodule is the identifying structural unit of hypertrophic scars and keloids. The nodule, which is absent from mature scars, contains high density of fibroblasts and unidirectional collagen fibrils aligned in a highly stressed orientation (Craig ,1973).

BIOCHEMICAL ANALYSIS OF ABNORMAL SCARS

Studies of collagen, proteoglycan and water content of keloids and hypertrophic scars compared with normal skin have shown interesting differences. Total collagen content has been measured by hydroxyproline estimation method and the proteoglycan content has been measured by glucosamine estimation method (Elson and Morgan, 1933).

Keloid tissue shows high levels of collagen, proteoglycan and water. The total collagen was fractionated into acid soluble and pepsin soluble portions and the

fractionated collagen was again estimated. Interestingly, here keloids show higher acid collagen than the pepsin soluble collagen. Hypertrophic scars and normal skin show higher pepsin soluble collagen. These observations show that though keloids show high amounts of collagen their cross linking is very poor as the pepsin soluble fraction represents the cross-linked collagen. Apart from collagen and proteoglycans, the synthesis of other extra cellular matrix proteins has also been found to be much higher in keloids and hypertrophic scars. Excess matrix accumulation can occur not only by increased synthesis of extracellular matrix components but also by a reduction in matrix degradation, either intracellular or extracellular. The ability of collagenases isolated from the scar fibroblast to degrade collagen has been studied with respect to hypertrophic scars and it has been shown that the activated hypertrophic scar fibroblasts have reduced ability to degrade collagen (Ghahary et al.,1998).

The release and activation of growth factors during the inflammatory phase of healing are pre-requisites for subsequent processes, including angiogenesis, re-epithelialization, recruitment and proliferation of fibroblasts and matrix deposition. Angiogenesis is stimulated by endothelial chemo- attractants and mitogens that are released by mast cells, neutrophils, macrophages and keratinocytes (Kiristy, 1993). Wound re-epithelialization occurs following the migration of epithelial cells from the wound margin and epidermal appendages within the wound bed and is enhanced by EGF, TGF-β. Fibroblast recruitment, proliferation and production of extra cellular matrix are influenced by the fibrogenic growth factors PDGF, IGF-I and TGF- β as well as basic fibroblast growth factor. These fibrogenic growth factors upregulate

extra cellular matrix production, increase the rate of proliferation and migration of fibroblast, and inhibit production of the proteases required to maintain the balance between production and degradation. TGF-β was initially isolated from human platelets but has since been shown to be produced at wound site by infiltrating lymphocytes, macrophages and fibroblasts. The TGF- β family consists of at least five highly conserved peptides, with TGF-β 1, TGF-β 2 , and TGF-β3 (Ando and Jense, 1993).

PATHOLOGICAL SCAR

Excessive scar tissue was described in the Smith Papyrus about 1700BC. Albright was the first to describe it in 1806. He described it as a cancer - like tumor and referred to it as cancroid later amending the term to cheloid. Alibert coined the term ***"cheloid***" from the Greek word for ***"crab Claw"(***Alibert,1961***).*** Cosman et al, (1961) documented the presentation, characteristics, and treatment of keloids in the first systematic review of keloids in 1961. Mancini and Quaife (1962), and later Peacock et al., (1970) delineated the clinical differences between keloids and hypertrophic scars**.**

Keloids are defined as scars within the skin that grow beyond the confines of the original wound. In contrast, hypertrophic scars are raised scars which remain within the boundaries of the wound.

Hypertrophic scars

The incidence of hypertrophic scars following surgery is about 40-70%, whereas it is higher (up to 91%) following burn injury ***(***Deitch et al, 983***).*** Several reports conclude that there is a substantial increased risk for hypertrophic scarring in burn wounds that take more than 21 days to heal. Hypertrophic scarring also occurs due to dynamic mechanical skin tension acting on the healing wound (e.g sternum,

deltoid and upper back (Curtis and Seehar, 1978***).*** The natural history of hypertrophic scars is that they regress with time after injury, leaving behind, however, an unsightly wide gap of thinned dermis between wound edges. A familial pattern in hypertrophic scarring is not described. However populations with higher skin melanin content are known to have a higher incidence of hypertrophic scars. These populations include Africans, Asians, and Hispanics (Lewis and Sun ,1990***).*** Hormonal influences are also known to be important factors, with hypertrophic scarring often initated at the start of puberty or during pregnancy. Scar tissue cells are senstitive to the influences of the same growth factors that drive normal tissue growth and development. Schierle et al., **(**1997*)* demonstrated an increase in testosterone receptors in hypertrophic scars, which may contribute to the formation of these scars during adolescence.

Figure: 2

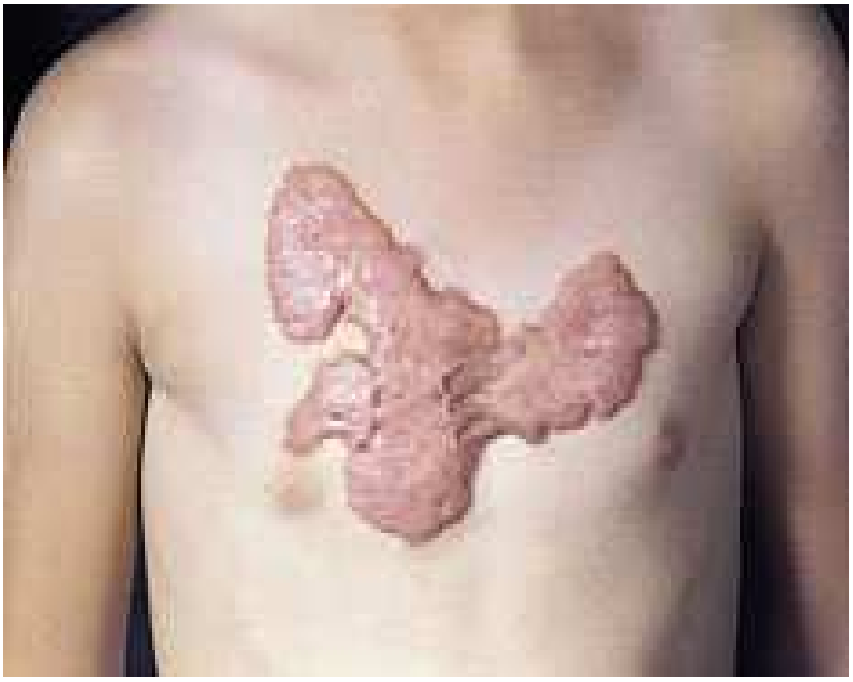
Keloid Scars

Although the diagnosis of keloids is often inappropriately applied to hypertrophic scars, the two lesions can be differentiated at several levels. Unlike hypertrophic scars, the natural history of keloids is that they do not regress with time following injury. Keloid tumors grow to reach a certain size and may remain that size indefinitely. Patients with keloids also have an associated strong family history of keloids. Both autosomal dominant and recessive modes of transmission have been reported. Castagnoli et al, (1990) reported an association between keloid occurrence and HLA-BW16, BW21, and BW35.Most evidence suggests that keloid scarring is a genetic anomaly (Saya et al., 1999). The genetic basis for this disease is evidenced by the abherrant behaviour of fibroblasts explanted from the scar tissue . Several investigators have demonstrated that the keloid fibroblasts exhibit abnormal regulation of apoptosis (Akasaka and Ishikawa ,2000). It has also been reported that keloid fibroblasts in vitro produce abnormally high levels of collagen, fibronectin, and proteoglycans, and display atypical responses to regulation by metabolic modulators, such as growth factors and hydrocortisone **(**Tredget et al., 1997**)**. McCauley et al, (1992) reported increased serum levels of inflammatory cytokines in patients with keloids. Histologically, collagen bundles are thicker and more abundant in keloids and form a cellular node –like structure in the deep dermis. Fibroblasts isolated from keloids and hypertrophic scar exhibit increased gene transcription of alpha 1 procollagen. (Ueda et al., 1999) .A strong correlation exists between keloid

formation and age and sex hormones, with Fibroblasts isolated from keloids and hypertrophic scar. younger individuals being more vulnerable to their development**.**

Figure :3

KELOID SCAR



Location

Keloids and hypertrophic scars are rarely found on the eyelids, genitalia, palms, or soles. Keloids do occur frequently, however, over the deltoid region, presternal area, and the upper back .They occur more frequently in areas where the skin is thick than in areas where the skin is thin (Crockett, 1964).

Age

Patients who developed keloids or hypertrophic scars as children or teenagers may not exhibit this tendency in later life. Ketchum et al, (1974) proposed reasons for this phenomenon: younger individuals are more frequently subjected to trauma and younger skin possesses greater tensions, whereas older skin is less elastic and has more redundancy .The rate of collagen synthesis also is greater in younger persons. (Utto 1970; Ketchum et al.,1974).

Race

Certain races such as Africans and Asians are more susceptible to hypertrophic scarring and keloid formation than Caucasians. Incidence ratios for the races vary from 5:1 to 15:1 (Cosman et al.,1961). Koonin (1964) suggested that an aberration of the metabolism of melanocyte stimulating hormone (MSH) may be responsible. He found deeply pigmented people of all races more prone to keloid formation than those with fair skin.

Scar Classification

Mature scar - Light colored and flat.

Immature scar - Red, sometimes itchy or painful, and slightly elevated in the process of remodelling. Many of these will mature normally over time and become flat.

Linear hypertrophic scar - (e.g. surgical or traumatic scar) Red, raised sometimes itchy scar confined to the border of the original surgical incisions .This usually occurs within weeks after surgery. These scars may increase in size rapidly for 3-6 months and then, after a static phase, begin to regress. They generally mature to have elevated, slightly rope-like appearance with increased width, which is variable. The full maturation process may take up to 2 years.

Wide spread hypertrophic scar (e.g. burn scar) A widespread red, raised sometimes itchy scar that remains within the border of the burn injury.

Minor keloids - Focally raised, itchy scar extending over normal tissue. This may develop up to 1 year after injury and does not regress on its own. Simple surgical excision is often followed by recurrence. There may be a genetic abnormality involved in keloid scarring, typical sites including ear lobes.

Major keloid – Large, raised (> 0.5cm) scar, possibly painful or pruritic and extending over normal tissue This often results from minor trauma and continues to spread over years (Thomas et al., 2002).

TREATMENT OF HYPERTROHIC SCAR AND KELOIDS

Reiffel (1995) has proposed the preventive use of adhesive sutures after any surgical incision. In a randomized controlled study, he demonstrated the utility of such preventive measures. A strategy of early clinical assessment can be considered as a good precautionary measure to prevent the pathologic evolution of scars, whatever be the origin of the scar and the intensity of the pathologic process. Regarding scar management, too many solutions have been proposed, some of which are inadequate. Reiffel concluded that silicone gel sheeting and intralesional corticosteroids are the only treatments for which sufficient evidence exists to make evidence based recommendations in the management of a wide variety of abnormal scars. Other standard practices and new emerging therapies need large scale studies with long term follow up before they can be recommended as alternative therapies. An appropriate classification of scars is a significant element because the differences in their clinical types determine the therapeutic approach. The existence of a variety of classification schemes is based on the need of optimal clinical reliability. Post-trauma wound healing leads to different types of scars: normal scar; wide-stretched scar, atrophic scar, scar contracture, hypertrophic scar and keloid.

Surgery

Surgical excision of hypertrophic scars or keloids is a common management option when used in combination with steroids with-or without silicone gel sheeting. However, excision of keloids on its own results in a high rate of recurrence of 45 to 50 % (Berman et al., 1997).

Radiation therapy

Radiation therapy has been used as monotherapy, and in combination with surgery, for hypertrophic scars and keloids. Response to radiotherapy alone is 10–94% with a keloid recurrence rate of 50–100% (Lawrence, 1991). Such high recurrence rates are understandable given the resistance of these cases to other management options. Best results have been achieved with 1500 to 2000 rads over 5 to 6 sessions in the early postoperative period (Norris, 1995). Most investigators agree that radiotherapy should be reserved for adults and for keloids resistant to other management modalities.

Laser Therapy

Laser therapy involves the use of high-energy light to burn away damaged skin. Laser may be used to minimize wrinkles and fine scars .The newer flash lamp pumped pulse dye laser selectively decreases scar blood flow. Therefore flash lamp pumped pulsed dye laser loses efficacy in dark skinned individuals, who are at high risk for keloids (Alster and West, 1995).

Cryotherapy

Cryotherapy is a technique that uses specialized equipment to freeze scar tissue using liquid nitrogen. Cryotherapy results in microcirculatory disturbances leading to tissue damage, especially fibroblasts. Limitations include the delay of several weeks required for postoperative healing and the commonly occurring side effect of permanent hypopigmentation (Malakar and Malakar, 2000).

Ultrasonic or microwave heating

Ultrasonic or microwave heating is used to soften the scar and decrease the tensile strength of a scar. It appears to reduce collagen content possibly by increasing collagenase activity, and some benefit is seen (Shamberger et al., 1981).

Pressure Therapy

Prolonged pressure on hypertrophic collagen has been reported to be effective in preventing recurrence of keloids after surgical treatment (Pollack, 1994). Garments made up of elasticized material are available for different anatomical areas of the body. Such garments are advised immediately after wound healing.

Silicone Gel Sheeting

Silicone gel sheeting has been a widely used clinical management option for hypertrophic scars and keloids since the early 1980s. Silicone gel sheeting may be especially useful in children and people who cannot tolerate the pain of other management procedures (Quinn, 1987). Some formulations of silicone oil have been

shown to be effective on minor hypertrophic scars although these studies have limitations in their design (Wong et al., 1996)

Scar Massage

This approach is usually combined with several other modalities. Massage therapy appears most beneficial in preventing contractures. However, massage also mechanically stimulates fibroblast synthesis of collagen (Car-Collins, 1992).

Adhesive Microporous Hypoallergenic Paper Tape

Applying paper tape with an appropriate adhesive to fresh surgical incisions for several weeks after surgery has been shown to be useful. The mechanism of this benefit is unknown, but may be mechanical and occlusive (Reiffel, 1995).

PHARMACOLOGICAL APPROACHES TO HYPERTROPHIC AND KELOID TREATMENT

Retinoids

Retinoids are synthetic derivatives of Vitamin A. Topical retinoids enhance epidermal proliferation while inhibiting proliferation of fibroblasts, and shift the healing process to normal regeneration. Adverse effects included photosensitivity, skin irritation in 50% of patients and skin atrophy in 10% of patients (Janssen, 1980).

Imiquimod Therapy

Imiquimod is a novel synthetic compound that is a member of the imidazoquinolone family of drugs. Imiquimod induces local production of interferons at the site of application. It is available as a 5% cream and is started immediately after surgery and continued daily for 8 weeks. The major side effect is mild to moderate irritation at the site of application. Hyperpigmentation occurs in 50 % of treated wounds (Jacob et al., 2003).

Tacrolimus

Tacrolimus is an immunomodulator that inhibits TNF-alpha. *gli*-1, an oncogene, has been found to be overexpressed in fibroblasts of keloids. Rapamycin, a close analogue of tacrolimus, was used in an in vitro study and was found to inhibit the *gli*-1 oncogene, thus giving a rationale to initiate clinical trials of topical tacrolimus and rapamycin. Although the results were not statistically significant, the study showed a decrease in induration, tenderness, erythema, and pruritus for most keloids *(*Kim et al., 2001).

Bleomycin

Bleomycin in the dose of 1.5 IU/ml injected intralesionally through multiple pricks resulted in flattening of lesions in 6 of 13 cases (Espana et al., 2001.*)* Similarly, bleomycin has also been tried by Bodokh and Brun (1996) intralesionally, at monthly intervals to treat keloids. It was found to be effective but caused many side effects. Moreover, its high cost is a limiting factor.

Vitamin E Cream

Vitamin E is sometimes recommended for the self – management of scars. However there is no clinical evidence to suggest that it is effective *(*Nachbar and Korting, 1995).

Interferon

Interferon α-2β, which has antiproliferative properties, was tried by Berman and Duncan (1989). They injected a keloid intralesionally with 1.5 million IU IFN α-2β twice a day for 4 days. The area of the keloid was found to be reduced to 50% of its original size by day 9. IFN α-2β when also used post-operatively reduced the rate of recurrence to 19 % as compared to that of intralesional steroid, where the recurrence rate was 51%.

Antihistamines

Histamine antagonists, especially H_1 antagonists, can relieve some of the burning and pruritus associated with keloids and may modulate keloid size. H_1 blockers also inhibit collagen synthesis (Cosman et al., 1982).

Pencillamine, β -Aminopropiontrile and Colchicine

Pencillamine, β -aminopropiontrile are lysyl oxidase inhibitors that interfere with collagen cross- linking, making collagen more susceptible to collagenases. These oral agents are used with colchicine which increases collagenase activity **(**Meenakshi et al., 2005).

Intralesional 5-fluorouracil

5-Fluorouracil injected intralesionally has been successfully used to treat small keloids. A mixture of 0.1 ml of triamcinolone acetonide (10 mg/ml) and 0.9 ml of 5-FU (50 mg/ml) produces the best results. It is injected into the keloid 3 times per week initially. Small keloids usually require a total of 5-10 injections given weekly. Painful injections are often the limiting factor. Recurrence is common after stopping the drug (Fitzpatrick, 1999).

Verapamil

Many organic calcium channel blockers (eg., verapamil) induce collagenase production and scar tissue degradation .They induce changes in fibroblast gene expression, resulting in decreased collagen synthesis and increased collagenase production . These effects appear to be mediated by interruption of the basic cellular G protein signal transduction pathway that is critical to regulation of fibroblast behavior *(*Doong et al., 1996).This pathway can be interrupted at multiple points by a wide range of commonly used drugs. Verapamil injected into the lesion has been shown to induce scar degradation in the skin, fascia and periocular tissue **(**Lee and Ping, 1994).

Triamcinolone

Corticosteroids are effective in the majority of non-infected scars that exhibit symptoms such as pain and pruritus. Intralesional corticosteroids are believed to act by inhibiting fibroblast growth and decreasing alpha2 macroglobulin

levels, which lead to collagen degradation. Corticosteroid preparations used for intralesional injection have included hydrocortisone, triamcinolone, and dexamethasone, with none proving to be particularly advantageous. Several concentrations between 10 and 40 mg/ml can be used. In steroid-sensitive areas (e.g. nose, eyelids, lips) that can undergo dermal atrophy, 10 mg/ml should be used initially. After the initial dose, the patient should return after 3 to 4 weeks, and the injection should be repeated at a similar or higher dose if required. The local adverse effects of steroid injections are associated with the dose given. These are hypopigmentation, dermal atrophy, telangiectasia, necrosis, and ulceration. A major disadvantage of using intralesional corticosteroid is the pain associated with the injection, which can lead to patient noncompliance during follow- up *(*Sclafani et al., 1996).

Inhibitors of Gene Transcription

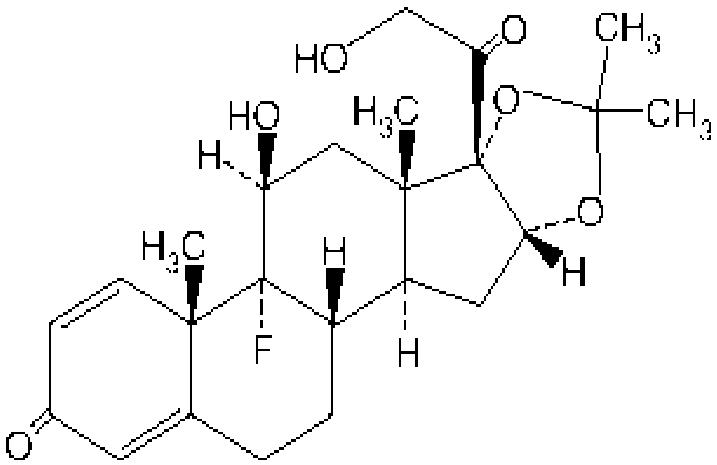
The antimetabolites mitomycin -c and 5- fluorouracil inhibit proliferation of cells by blocking DNA synthesis and transcription by competitive inhibition of thymidylate synthesis ***(***Fitzpatrick, 1999***)***. A single application in the first few days after wound closure appears to be effective. Antimetabolite - induced apoptosis has also been demonstrated in Tenon's capsule fibroblasts (Crowston, 1998).

Growth factor inhibition.

The transforming growth factor (TGF-β) family of proteins is centrally involved in regulating wound healing. The process of TGF-β synthesis and release is activated by injury and, along with the platelet-derived growth factor; it has a central and critical role in the induction of wound healing. The binding of TGF-β to its receptor on fibroblasts causes fibroblast proliferation, extracellular matrix and structural protein synthesis and TGF-β synthesis. Mannose-6-phosphate and several other disaccharides sterically limit TGF-β binding to its receptor and limit scar formation in experimental wound-healing models (Ferguson, 1994).

PHARMACOLOGY OF DRUGS USED IN PRESENT STUDY

Triamcinolone



Triamciniolone structure

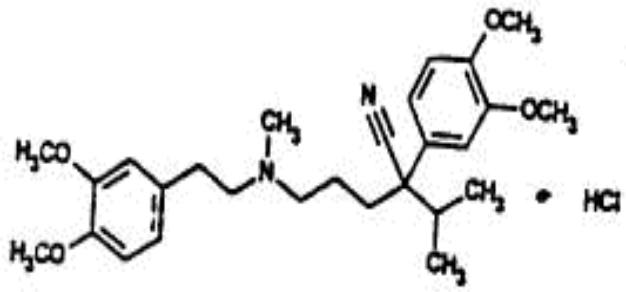
Intralesional steroid, namely, triamcinolone, is the most effective and widely used treatment for keloids. Triamcinolone acetonide is a potent anti- inflammatory corticosteriod and is a first line therapeutic drug for keloids. Large trials conducted in the 1960s and 1970s demonstrated that triamcinolone acetonide was effective in healing keloids in more than 80 % of cases *(*Hirshowitz et al., 1982*).* Triamcinolone inhibits the proliferation of normal fibroblasts and fibroblasts in keloids. It inhibits

collagen synthesis, increases collagenase production, and reduces tissue levels of collagenase inhibitors. Steroids also induce ultrastructural changes in collagen synthesis that enhance the organization of collagen bundles and degenerate the characteristic keloidal collagen nodules. Despite relatively few randomised, prospective studies there is a broad consensus that injected triamcinolone is effective for the treatment of keloids and hypertrophic scars and should be the first-line therapy for the treatment of keloids and second-line therapy for the treatment of hypertrophic scars if other other treatments have failed (Alster and Willams, 1997; Griffith et al., 1970).

Results are improved when corticosteroids are combined with other therapies such as surgery (Tang, 1992) and cryotherapy (Whang et al., 1997). Intralesional corticosteroid injection is associated with injection pain, even with standard doses of insoluble triamcinolone (40 mg/ml), and up to 63% of patients experience adverse effects that include skin atrophy, depigmentation and telangiectasias (Sproat et al., 1992). Topical steroid creams have been used with varying success, but absorption through an intact epithelium into the deep dermis is limited. A prospective, randomised study showed that topical steroids do not reduce scar formation in post-burn deformities (Yii, 1996).

Calcium channel blockers

Verapamil



Verapamil structure

Hypertrophic scars and keloids are characterized by the overproduction and increased deposition of extracellular-matrix proteins such as laminin, fibronectin, and collagen. The metabolism of cellular calcium ions (i.e., the intracellular concentration) may contribute to this production.

Five calcium channel blockers (amlodipine, felodipine, manidipine, diltiazem, verapamil) significantly decrease collagen deposition in the extracellular matrix and inhibit the expression of various collagens (I, III, IV) in vitro. In addition to that, calcium channel blockers specifically increase the proteolytic activity of one type of collagenase (IV) (Huang et al., 1999).

Verapamil, a widely used calcium channel blocker, has been shown to inhibit synthesis of extracellular matrix molecules, including collagen, glycosaminoglycans, and fibronectin .In addition, calcium channel blockers have been reported to increase collagenase and transforming growth factor -β activity (Rehman et al., 1998). Lee and Ping (1990) reported that treatment of the fibroblast - populated collagen matrix with L- type voltage - gated calcium channel blockers, verapamil hydrochloride, 100μmol/L reduced the incorporation of tritrated proline into the extra cellular matrix of the fibroblast - populated collagen matrix by almost 50 to 60%.

Verapamil has been shown to stimulate procollagenase synthesis in keloids, hypertrophic and cultured normal human fibroblasts, resulting in depolymerization of actin filaments, alteration of their cell shape, and reduction of fibrous tissue production ***(***Doong et al., 1996***).*** Calcium antagonists alter cell shape and induce procollagenase synthesis in keloids and normal human dermal fibroblasts. The first successful results of the intralesional injection of verapamil were presented in 1994 in burn scars (Lee et al., 1994).

Verapamil hydrochloride was used for the treatment and prevention of recurrence of keloid and burn scars by local intralesional infiltration (D'Andrea et al., 2002***).*** For stabilized keloids the results are poor compared to topical steroids. However, when verapamil was used following surgical excision of the keloid (2.5 mg/ml with doses ranging from 0.5 to 2.0 ml depending on the size) on postsurgical days 7, 14, 28, and during the second month, and combined with topical silicone layering without pressure therapy, there was a 54 % cure rate with absence of recurrence after 18 months (Eray Copcu et al., 2004)

METHODOLOGY

The study used a randomized, single blind parallel design to compare the effect of the calcium channel blocker verapamil and the corticosteroid triamcinolone on the healing of hypertrophic scars and keloids in two groups comprising 27 patients each. Patients who satisfied the selection criteria and gave written informed consent to participate in the study were chosen for the study.

PATIENT SELECTION CRITERIA

Inclusion criteria used :

- Age between 10 years and 50 years
- Atleast one hypertrophic scar or keloid
- Scar on the body of size > 2 cm and < 10 cm.
- Hypertrophic scar or keloid of less than 5 years duration

Types of scar that were included were due to :

- Flame and acid burns
- Wounds due to trauma or surgery
- Insect bite
- Acne

Exclusion criteria :

- Family history of keloids
- Dark pigmented skin
- Pregnancy or lactation
- Patients with other systemic illnesses like diabetes mellitus, cancer, mental disorders and cardiac diseases
- Patients from outside Vellore District, Tamil Nadu

Study Design Used:

Patients were randomly allocated to receive intralesional injection of either 1ml of verapamil (2.5mg) or 1ml of triamcinolone (40mg) once in 3 weeks. Clinical assessment of the scars were performed at the beginning of the study and at 3 week intervals after starting treatment. The drugs were administered till the scar flattened or for a maximum period of 6 months. The patients were asked to return for scar examination after 1year to check for any recurrence or complication

The clinical assessment of the scar was based on the Vancouver Scar Scale which is the standard scale used universally for scar assessment (Mary Jo Baryza et al., 1995). This scale was slightly modified for the Indian patients. The scale scores the scars on four parameters namely pigmentation, vascularity , pliability, and height. In addition, the scar length, width and height also were measured using a centimeter scale ..

At each visit the patients' scars were photographed on a digital camera Nikon coolpix 3200.The patients were also given a proforma to assess their own response to the treatment they received in terms of itching, pain and color changes. This was mainly subjective.

This study was conducted in the outpatients Department of Plastic and Reconstructive Surgery at the Christian Medical College and Hospital, Vellore.

Determination of Sample Size:

The sample size for the study was calculated to be 27 in each group on the basis of the alpha error of 0.05% (power of the study was 80%). This data is expressed as Mean ± S.E.

Statistical Analysis of Data :

For each study parameter in each group the mean value and standard error of mean (SEM) was calculated. The Wilcoxon Signed Rank Test was used for all statistical analyses of the data. Kaplan Meier graphs & log rank test were done to compare the rate at which all the study parameters reduced to zero (zero is considered as the event), with the two drugs . A *P* value of less than 0.005 was considered to be statistically significant.

RESULTS

54 patients fulfilled the selection criteria of the study and were selected for the study. Of these, 27 were randomly allocated to receive triamcinolone and the other 27 were allocated to receive verapamil .The four parameters that were measured according to the modified Vancouver scale were Pigmentation, Vascualarity, Pliability and Height. The Vancouver scale and modified Vancouver Scale are included in the Annexure (Annexure 4).

The demographic details of the two study groups are shown in Figure 4a, 4b and 5a, 5b. The mean age of the patients in the verapamil group was 26years and that in the triamcinolone group was 20 years. The male and female ratio in both study groups was the same .The etiology of scars of patients in both study groups is shown in Table 1.The location of scars of patients in both the groups is shown in Table 2.

Each parameter of Vancouver scale were studied and were compared within the study groups serially upto 24 weeks and follow up was done after 52 weeks. Tables : 3a, 3b, 3c and 3d shows the effect of verapamil on the Vancouver scale parameters. The effects of triamcinolone is shown in Tables 4a, 4b, 4c and 4d . In both study groups there was a reduction in vascularity, pliability and height (Tables: 3b, 3c and 3d for Verapamil and Tables 4b, 4c and 4d for triamcinolone) during every third week .This reduction was maintained at 52 weeks also in the both study groups .A desired change in pigmentation was not seen with either of the two drugs(Table: 3a for verapamil and Table 4a for triamcinolone). In fact with triamcinolone , hyper pigmentation or hypo pigmentation were noticed in 25% of patients(Annexure 8 & 9).

Reduction in length, width and height as measured with a centimeter scale was studied in both groups during every 3rd week. Table 5 a, 5b and 5c show the effects of verapamil and Tables 6a, 6b and 6c show the triamcinolone effects There was reduction in width and height of the scar during every 3rd week in both groups. Length of the scar did not show any significant change in both the groups.

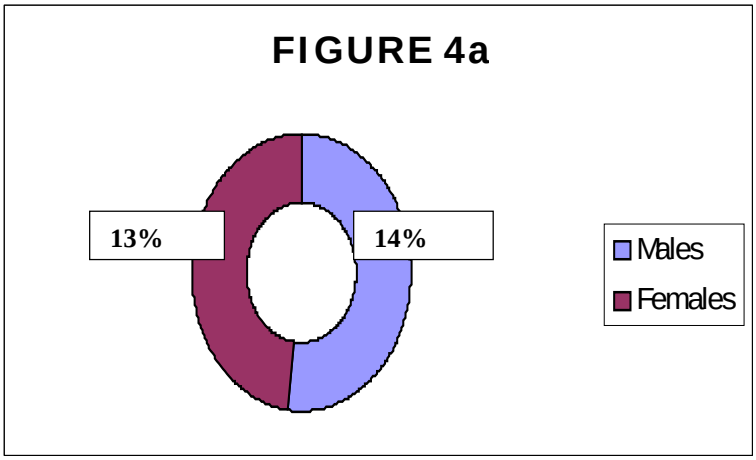
The median time taken for reduction of all the parameters to zero was compared between the two drugs. Figures 6a, 6b, 6c and 6d compares the parameters of Vancouver scale and Figures 7a, 7b and 7c compares the parameters measured with a centimeter scale. Figure 6a shows that while comparing the median time taken for pigmentation to reduce to zero, there was no significant difference between the two drugs. Figures 6 b, 6 c and 6 d show that the median time taken for reduction to zero in vascularity, pliability and height with triamcinolone was less as compared to verapamil and the difference was found to be significant. Figure 7a shows that the median time taken for reduction to zero in length is not significant in both the groups .Figure 7b and 7 c shows that the median time taken for reduction to zero in width and height as measured with triamcinolone was less as compared to verapamil and the difference was found to be significant .

Adverse drug reaction experienced by patients in each study groups are shown in Figure 8 and 9. Severe pain at injection site, hypopigmentation, irregular menstrual cycles and profuse sweating were complications observed with triamcinolone while profuse sweating and mild pain at the site of injection were seen with verapamil. Figure 10a , 10b and 10c represent one patient's photograph in the verapamil group and Figure 11a , 11b and 11c represent one patient's photograph in the triamcinolone group.

FIGURE 4

Demographic Details of Verapamil Study Subject (n=27)

Sex Distribution



Age Distribution

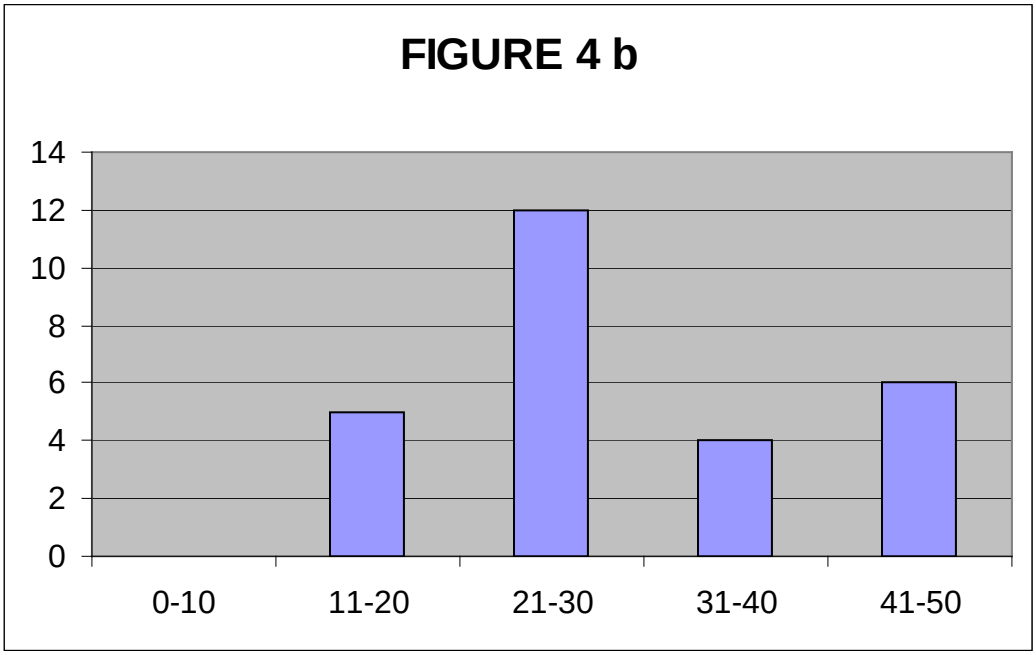
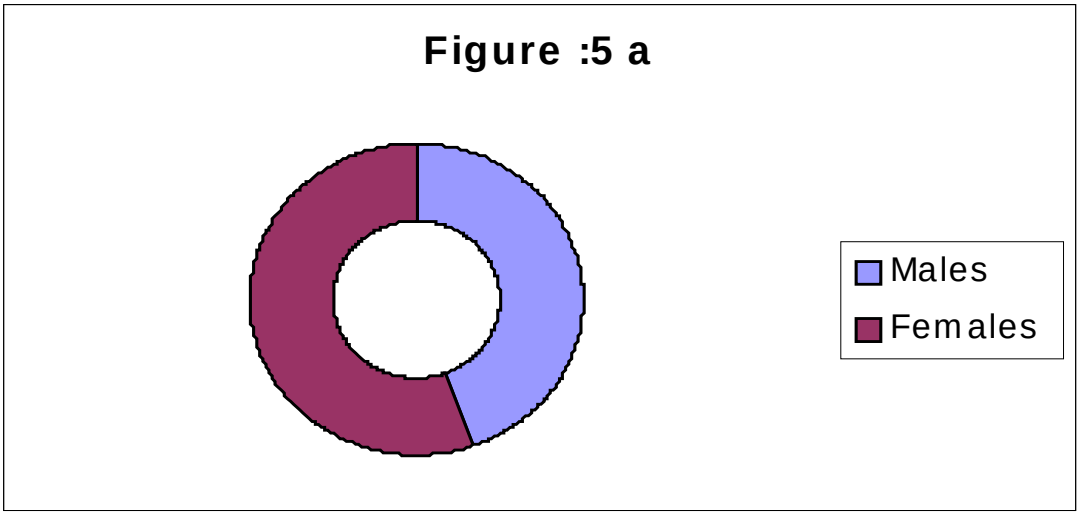


FIGURE: 5

Demographic Details of Triamcinolone Study Subjects (n=27)

Sex Distribution



Age Distribution

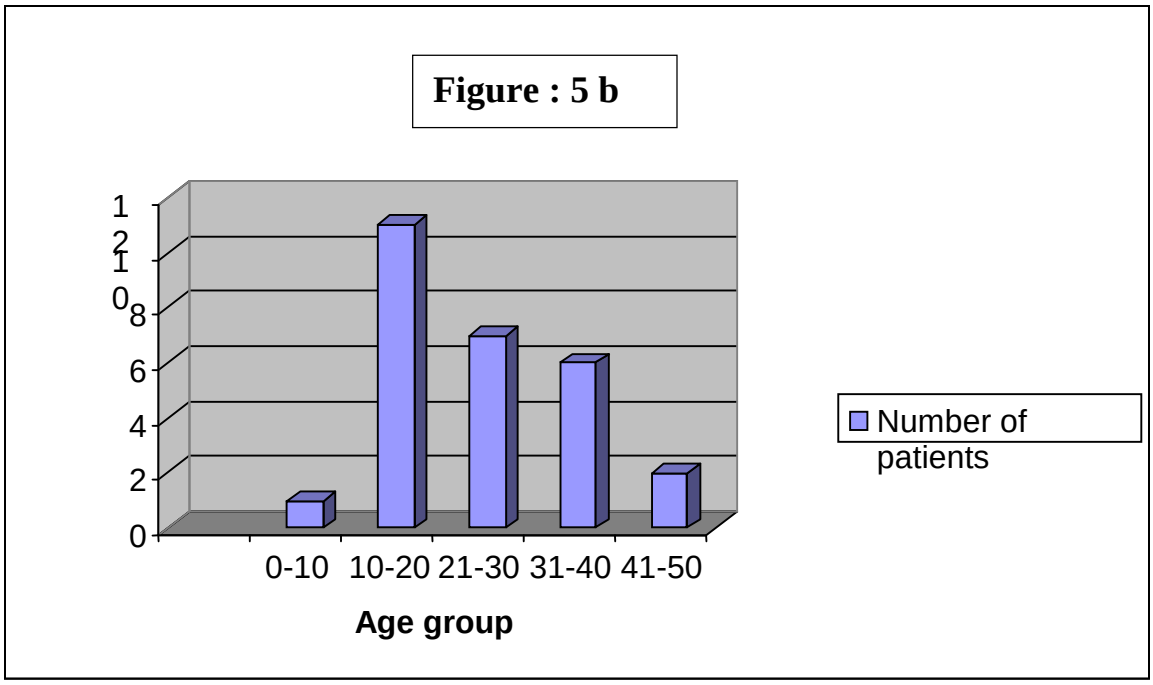


TABLE 1

ETIOLOGY OF SCARS IN EACH STUDY GROUP

	Triamcinolone group (n=27)	Verapamil group (n=27)
Pimple	**9**	**9**
Ear piercing	**7**	**4**
Road traffic accident	**7**	**11**
Surgery	**4**	**2**
Post-vaccination	**0**	**1**

TABLE 2

LOCATION OF SCARS IN EACH STUDY GROUP

	Triamcinolone	Verapamil
Face/Neck	**2**	**4**
Ear lobe	**7**	**2**
Sternum	**8**	**4**
Abdomen/Chest	**2**	**4**
Upper limb	**5**	**10**
Lower limb	**2**	**3**

VANCOUVER SCAR SCALE

TABLE No. 3 a

EFFECTS OF VERAPAMIL ON SCAR PIGMENTATION

(n= 27 in each group)

Verapamil

Weeks	0 wk	3 wk	9 wk	18wk	24wk	52wk
Mean (SEM in mm)	2(0)	1.78(0.11)	0.04(0.03)	0(0)	0(0)	0(0)
***p* value**	-	0.063[a]	0[a]	0[a]	0[a]	NS[b]

a : Compared to 0 week value
b : Compared to 24 week value

NS: Not significant ($p > 0.005$)

TABLE No.3 b

EFFECT OF VERAPAMIL ON SCAR VASCULARITY

(n= 27 in each group)

Verapamil

Weeks	0 wk	3 wk	9 wk	18wk	24wk	52wk
Mean(SEM) in mm	1.81(0.16)	1.37(0.09)	0.26(0.08)	0(0)	0(0)	0(0)
p Value	-	0.001[a]	0[a]	0[a]	0[a]	NS[b]

a : Compared to 0 week value
b : Compared to 24 week value

NS : Not significant ($p > 0.005$)

VANCOUVER SCAR SCALE

TABLE No. 3 c

EFFECT OF VERAPAMIL ON SCAR PLIABILITY

(n= 27 in each)

Verapamil

Weeks	0 wk	3 wk	9 wk	18wk	24wk	52wk
Mean (SEM) in mm	2.33(0.14)	1.56(0.12)	0.3(0.09)	0(0)	0(0)	0(0)
p Value	-	0[a]	0[a]	0[a]	0[a]	NS[b]

a : Compared to 0 week value
b : Compared to 24 week value

NS : Not significant ($p > 0.005$)

TABLE No. 3 d

EFFECT OF VERAPAMIL ON SCAR HEIGHT

(n= 27 in each)

Verapamil

Weeks	0 wk	3 wk	9 wk	18wk	24wk	52wk
Mean(SEM in mm)	1.63(0.09)	1.26(0.1)	0.19(0.07)	0(0)	0(0)	0(0)
p Value	-	0.002[a]	0[a]	0[a]	0[a]	NS[b]

a : Compared to 0 week value
b : Compared to 24 week value

NS : Not significant ($p > 0.005$)

VANCOUVER SCAR SCALE

TABLE No.4 a

EFFECTS OF TRIAMCINOLONE ON SCAR PIGMENTATION (n=27 in each group)

Triamcinolone

Weeks	0 wk	3 wk	9 wk	18wk	24wk	52wk
Mean (SEM) in mm	2(0)	1.52(0.14)	0.22(0.14)	0.22(0.09)	0.22(0.09)	0.22(0.09)
***p* value**	-	0.004[a]	0[a]	0[a]	0[a]	NS[b]

a : Compared to 0 week value
b : Compared to 24 week value

NS : Not significant ($p > 0.005$)

TABLE No.4 b

EFFECT OF TRIAMCINOLONE ON SCAR VASCULARITY (n= 27 in each group)

Triamcinolone

Weeks	**0 wk**	**3 wk**	**9 wk**	**18wk**	**24wk**	**52wk**
Mean (SEM in mm)	1.89(0.09)	1.15(0.1)	0.07(0.05)	0(0)	0(0)	0(0)
p Value		0[a]	0[a]	0[a]	0[a]	NS[b]

a : Compared to 0 week value
b : Compared to 24 week value

NS : Not significant ($p > 0.005$)

VANCOUVER SCAR SCALE

TABLE No.4 c

EFFECT OF TRIAMCINOLONE ON SCAR PLIABILITY

(n= 27 in each)

Triamcinolone

Weeks	0 wk	3 wk	9 wk	18wk	24wk	52wk
Mean (SEM) in mm	2.26(0.11)	1.3(0.1)	0.04(0.03)	0(0)	0(0)	0(0)
p Value	-	0[a]	0[a]	0[a]	0[a]	NS[b]

a : Compared to 0 week value
b : Compared to 24 week value

NS : Not significant ($p > 0.005$)

TABLE No.4 d

EFFECT OF TRIAMCINOLONE ON SCAR HEIGHT

(n= 27 in each)

Triamcinolone

Weeks	0 wk	3 wk	9 wk	18wk	24wk	52wk
Mean (SEM) in mm	1.67(0.1)	1.19(0.1)	0.07(0.05)	0(0)	0(0)	0(0)
p value	-	0.001[a]	0[a]	0[a]	0[a]	NS[b]

a : Compared to 0 week value
b : Compared to 24 week value

NS : Not significant ($p > 0.005$)

CENTEMETER SCALE
TABLE No.5 a

EFFECTS OF VERAPAMIL ON SCAR LENGTH
(n= 27 in each group)
Verapamil

Weeks	0 wk	3 wk	9 wk	18wk	24wk	52 wk
Mean (SEM) in mm	27.8(2.33)	23.3(2.28)	15.4(1.95)	12.4(1.66)	12.4(1.66)	12.4(1.66)
p value	-	0[a]	0[a]	0[a]	0[a]	NS[b]

a : Compared to 0 week value
b : Compared to 24 week value

NS : Not significant *(p* > 0.005)

TABLE No. 5 b

EFFECT OF VERAPAMIL ON SCAR WIDTH

(n= 27 in each group)

Verapamil

Weeks	0 wk	3 wk	9 wk	18wk	24wk	52wk
Mean (SEM) in mm	6.59(0.48)	5.26(0.54)	2.59(0.43)	1.81(0.25)	1.81(0.25)	1.81(0.25)
p value	-	0[a]	0[a]	0[a]	0[a]	NS[b]

a : Compared to 0 week value

b : Compared to 24 week value

NS : Not significant (*p* > 0.005)

CENTEMETER SCALE
TABLE No. 5 c

EFFECTS OF VERAPAMIL ON SCAR HEIGHT

(n= 27 in each group)

Verapamil

Weeks	**0 wk**	**3 wk**	**9 wk**	**18wk**	**24wk**	**52wk**
Mean(SEM) in mm	4.33(0.19)	3.229(0.2)	1.11(0.18)	0.15(0.07)	0.15(0.07)	0.15(0.07)
***p* value**	-	0[a]	0[a]	0[a]	0[a]	NS[b]

a : Compared to 0 week value
b : Compared to 24 week value

NS : Not significant ($p > 0.005$ **)**

CENTEMETER SCALE
TABLE No. 6 a

EFFECTS OF TRIAMCINOLONE ON SCAR LENGTH

(n= 27 in each group)

Triamcinolone

Weeks	0 wk	3 wk	9 wk	18wk	24wk	52 wk
Mean (SEM) in mm	27.1(2.65)	21.5(2.59)	14.4(1.97)	13.6(1.93)	13.6(1.93)	13.6(1.93)
p value	-	0[a]	0[a]	0[a]	0[a]	NS[b]

a : Compared to 0 week value
b : Compared to 24 week value

NS : Not significant ***(*** $p > 0.005$ ***)***

TABLE No. 6 b

EFFECT OF TRIAMCINOLONE ON SCAR WIDTH

(n= 27 in each group)

Triamcinolone

Weeks	**0 wk**	**3 wk**	**9 wk**	**18wk**	**24wk**	**52wk**
Mean(SEM)in mm	6.89(0.51)	3(0.26)	0.33(0.11)	0(0)	0(0)	0(0)
p value	-	0[a]	0[a]	0[a]	0[a]	NS[b]

a : Compared to 0 week value

b : Compared to 24 week value

NS : Not significant ($p > 0.005$ *)*

CENTEMETER SCALE

TABLE NO 6 c

EFFECTS OF TRIAMCINOLONE ON SCAR HEIGHT

(n= 27 in each group)

(Plastic Scale)

Triamcinolone

Weeks	**0 wk**	**3 wk**	**9 wk**	**18wk**	**24wk**	**52wk**
Mean(SEM) in mm	4.52(0.17)	2.56(0.12)	0.22(0.08)	0(0)	0(0)	0(0)
***p* value**	-	0[a]	0[a]	0[a]	0[a]	NS[b]

a : Compared to 0 week value

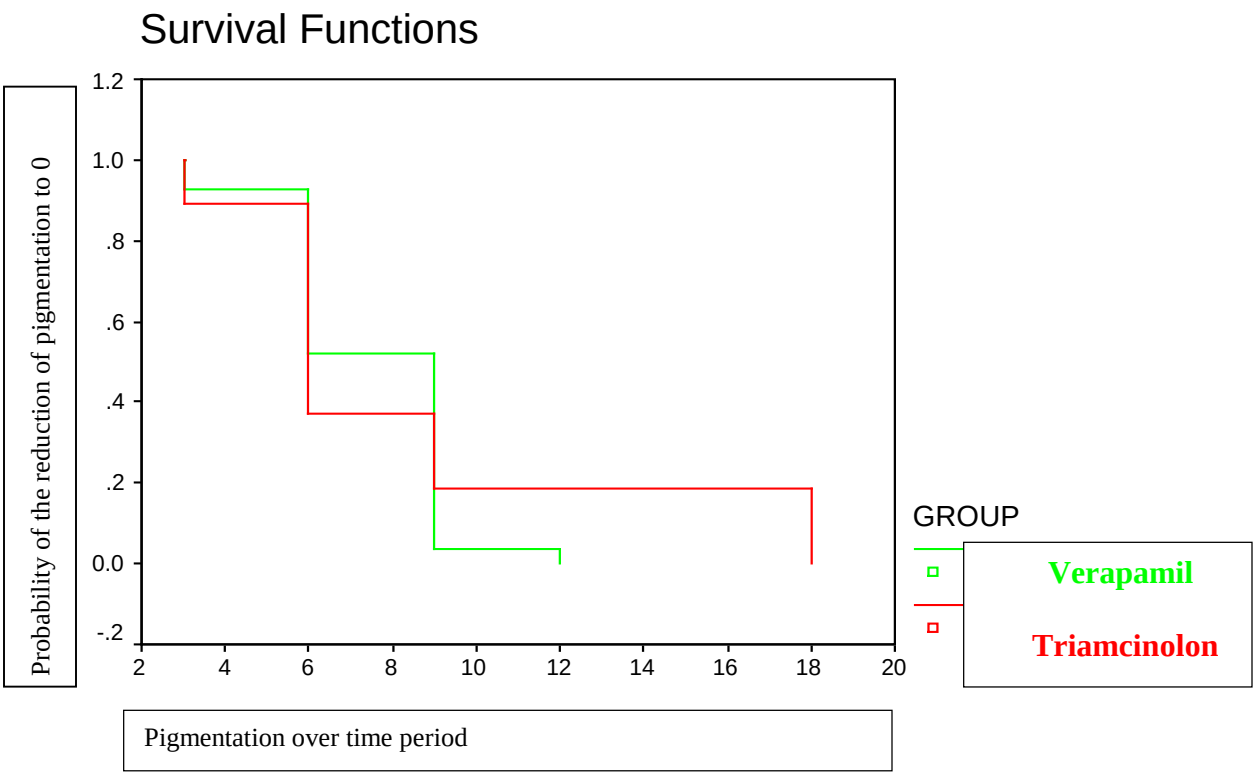
b : Compared to 24 week value

NS : Not significant ($p > 0.005$)

KAPLAN MEIER GRAPHS SHOWING THE RATE OF REDUCTION OF PARAMETERS BETWEEN THE TWO GROUPS BASED ON VANCOUVER SCALE.

Figure 6a

PIGMENTATION

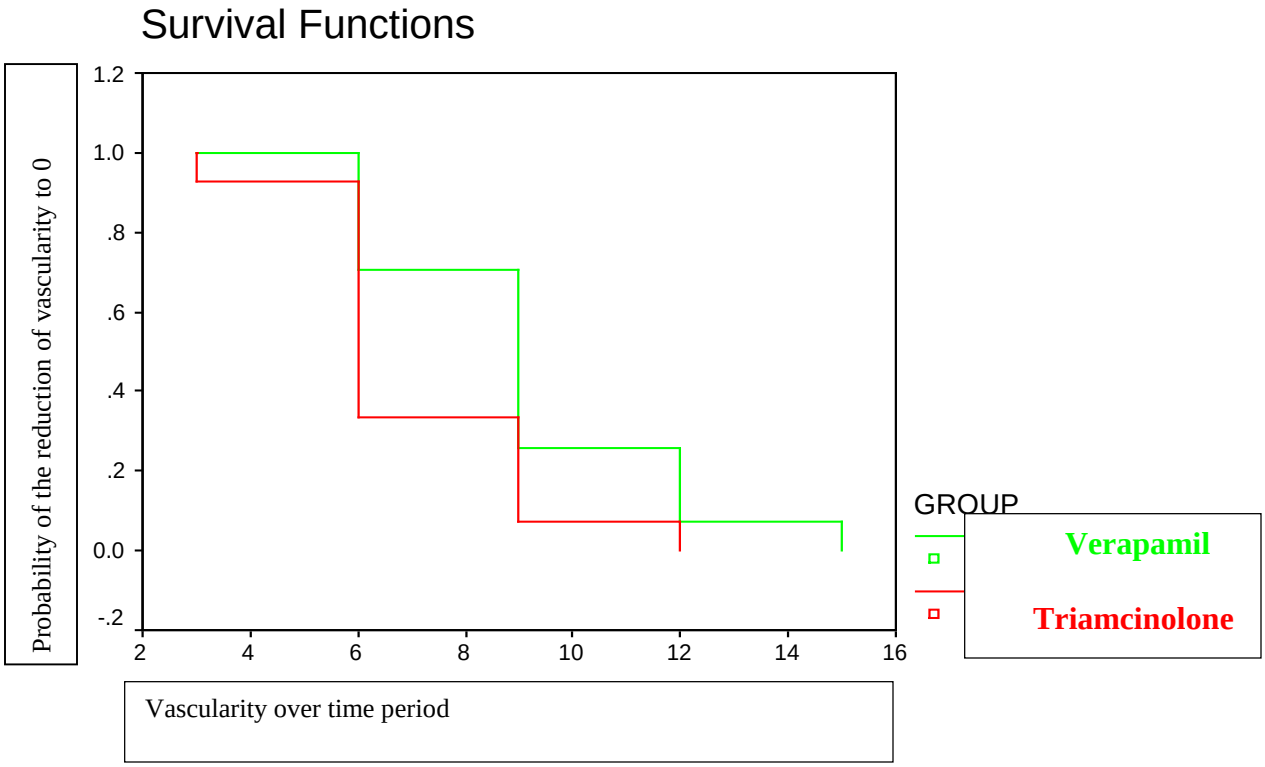


	Median survival time	95% Confidence Interval
Group TRI	6	(5,7)
Group VER	9	(9,9)

P value : .9147

Figure 6b

VASCULARITY

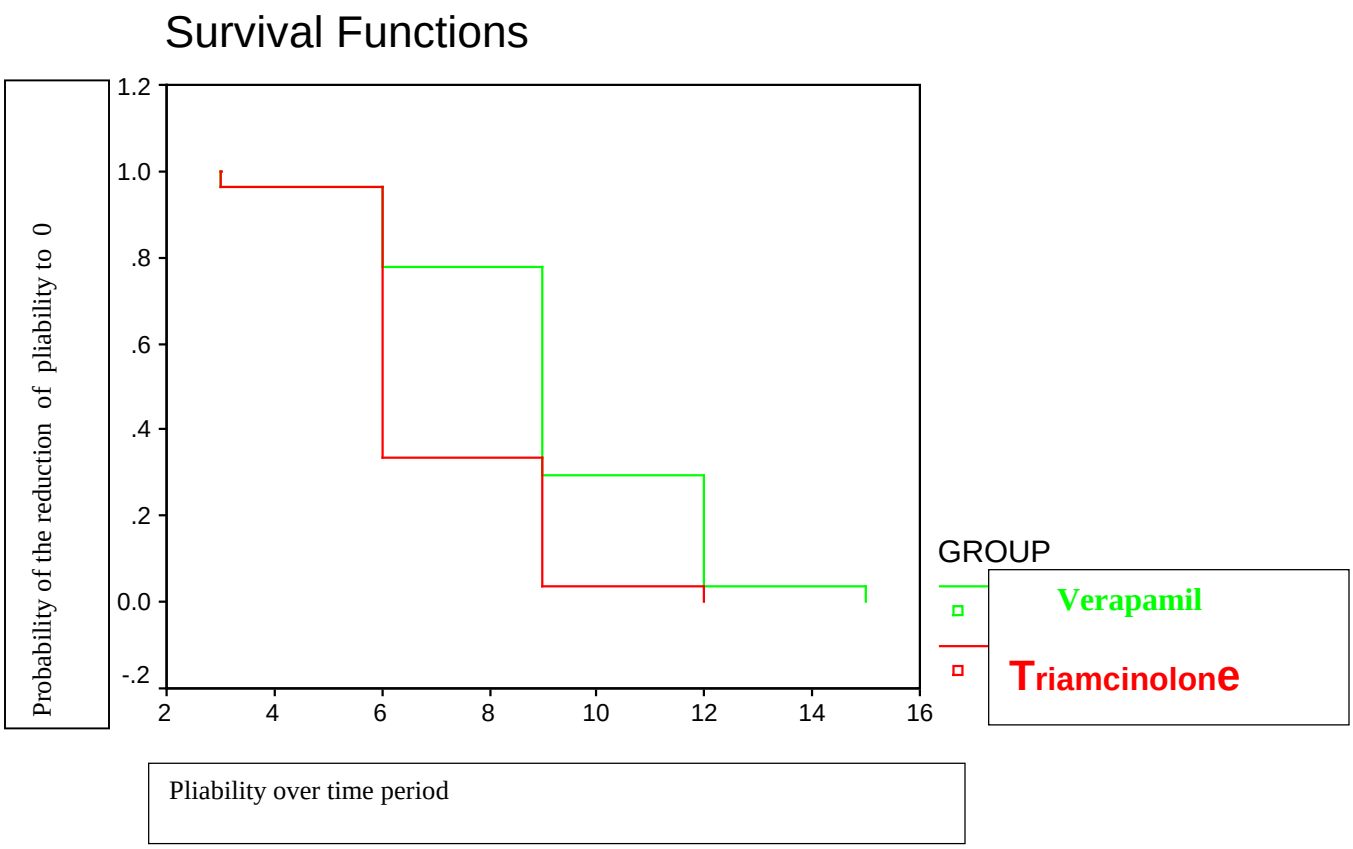


	Median survival time	95% Confidence Interval
Group TRI	6	(5,7)
Group VER	9	(8,10)

***P* value : 0.0032**

Figure 6c

PLIABILITY

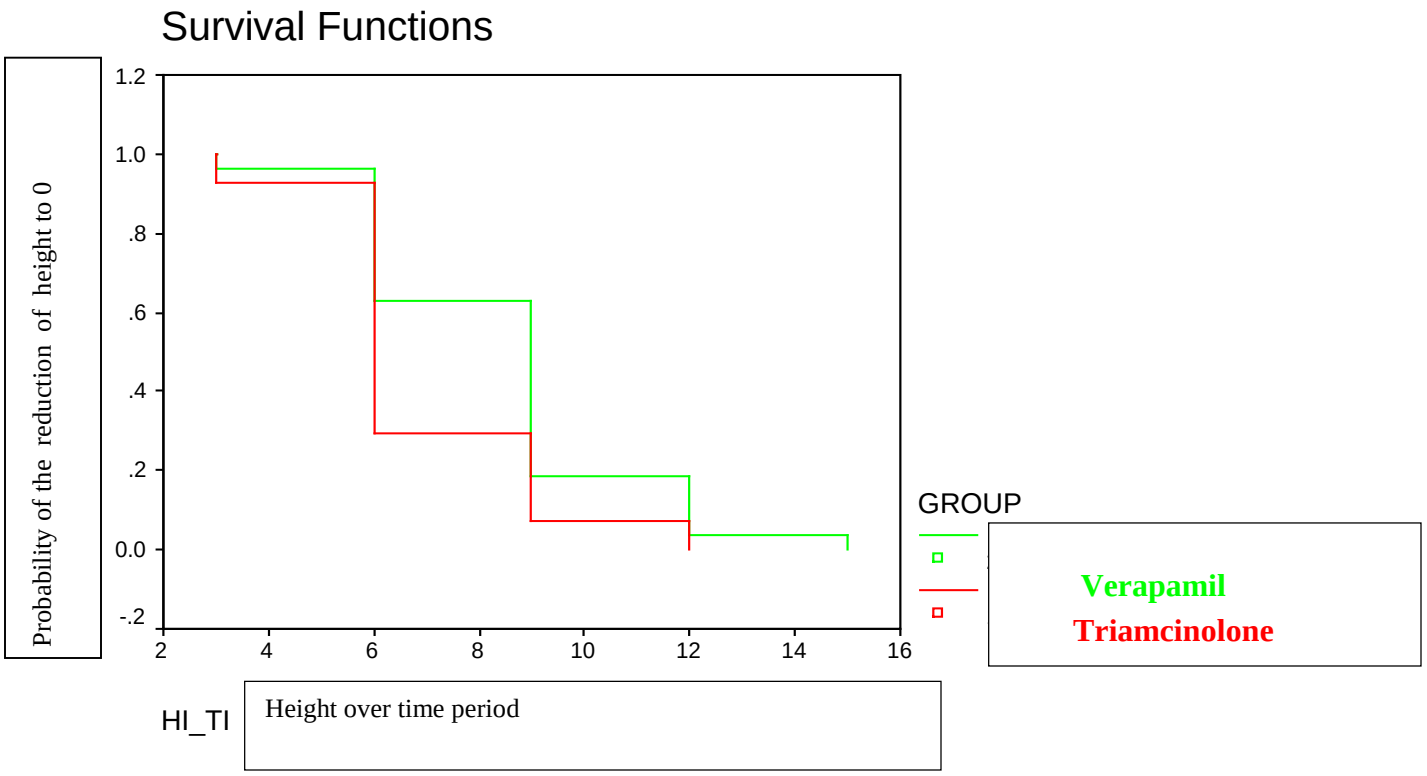


	Median survival time	95% Confidence Interval
Group TRI	6	(5,7)
Group VER	9	(8,10)

***P* value : .0006**

Figure 6d

HEIGHT



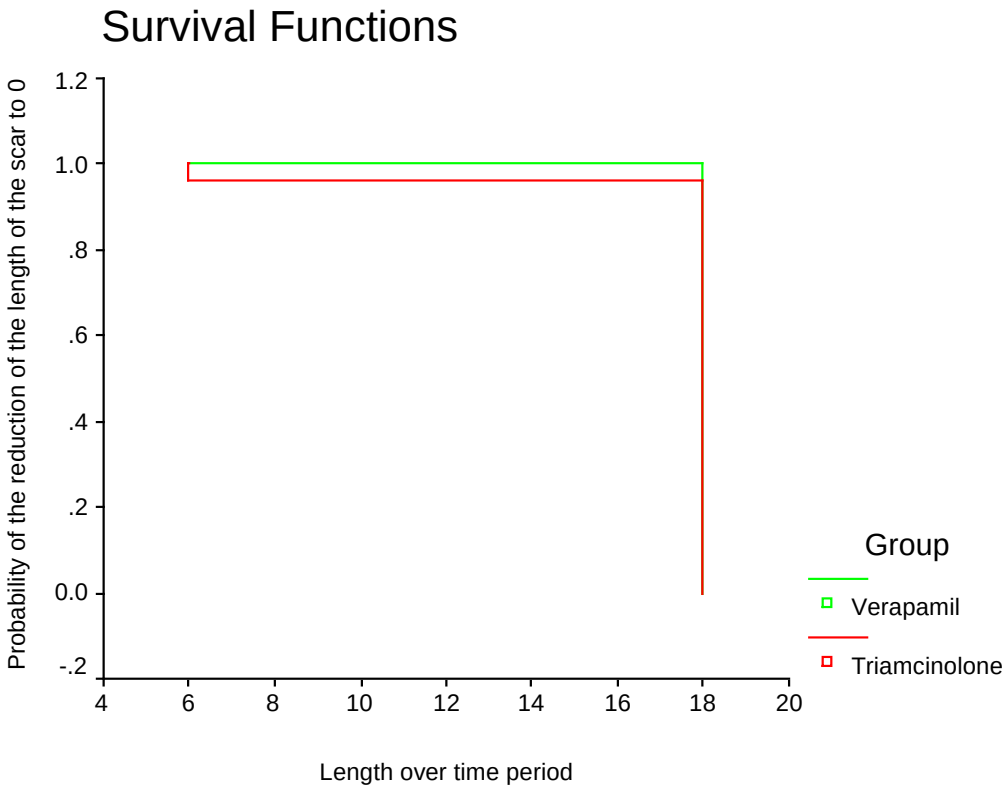
	Median survival time	95% Confidence Interval
Group TRI	6	(5,7)
Group VER	9	(8,10)

***P* value : 0.0187**

KAPLAN MEIER GRAPHS SHOWING THE RATE OF REDUCTION BETWEEN THE TWO GROUPS AS MEASURED WITH A CENTEMETER SCALE.

Figure : 7 a

LENGTH OF SCAR

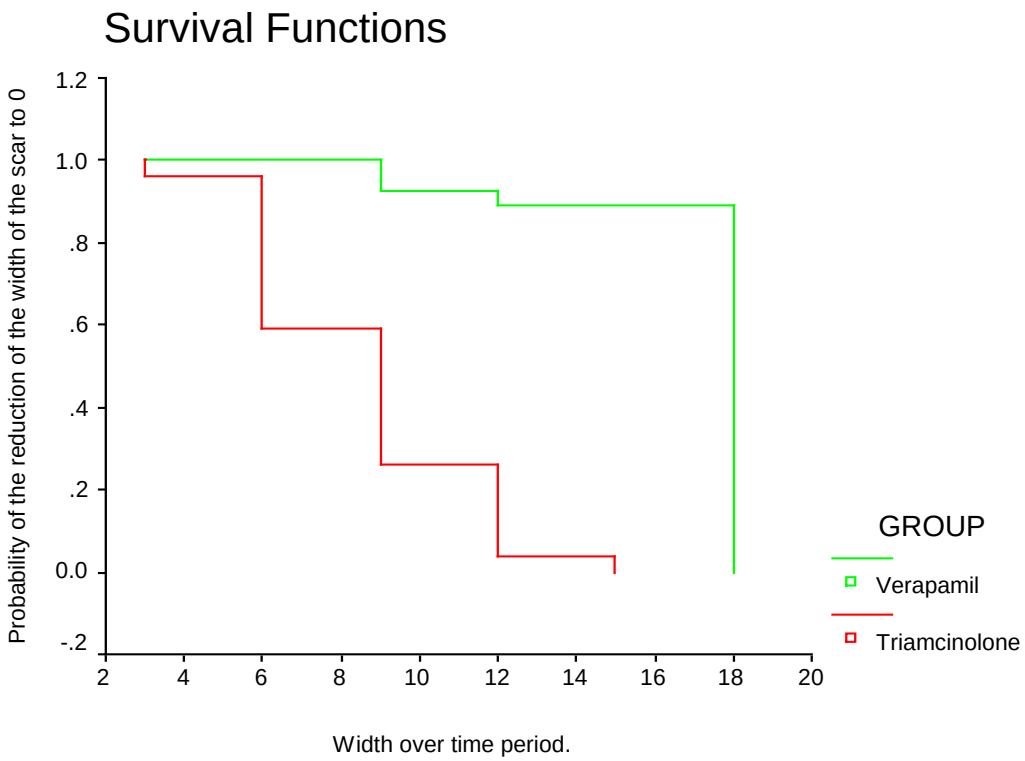


	Median survival time	95% Confidence Interval
Group TRI	18	(17,18)
Group VER	18	(18,18)

***P* value : 0.3173**

Figure : 7 b

WIDTH OF SCAR

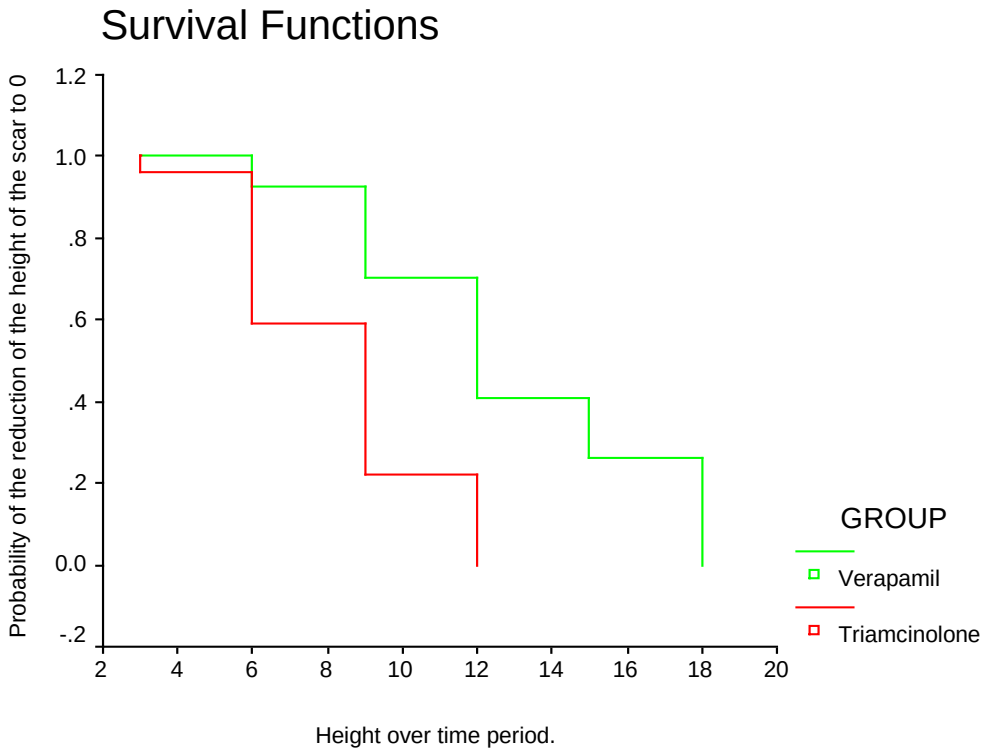


	Median survival time	95% Confidence Interval
Group TRI	9	(8,10)
Group VER	18	(16,18)

***P* value : 0.0000**

Figure : 7 c

HEIGHT OF SCAR



	Median survival time	95% Confidence Interval
Group TRI	9	(8,10)
Group VER	12	(10,14)

***P* value : 0.0000**

ADVERSE DRUG REACTIONS COMPARE BOTH THE GROUPS(N=27)

Figure-8

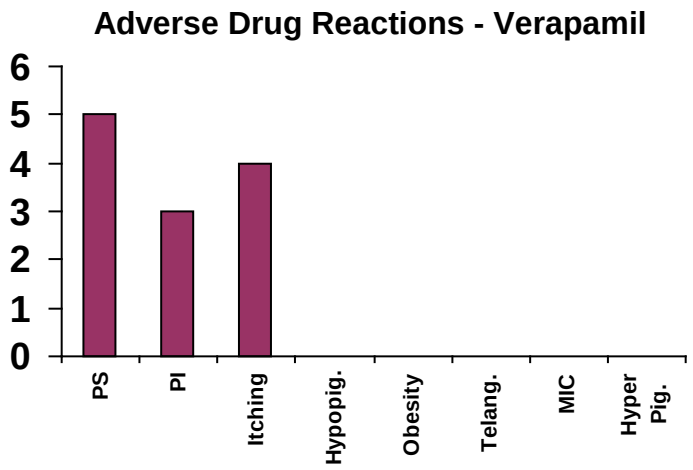
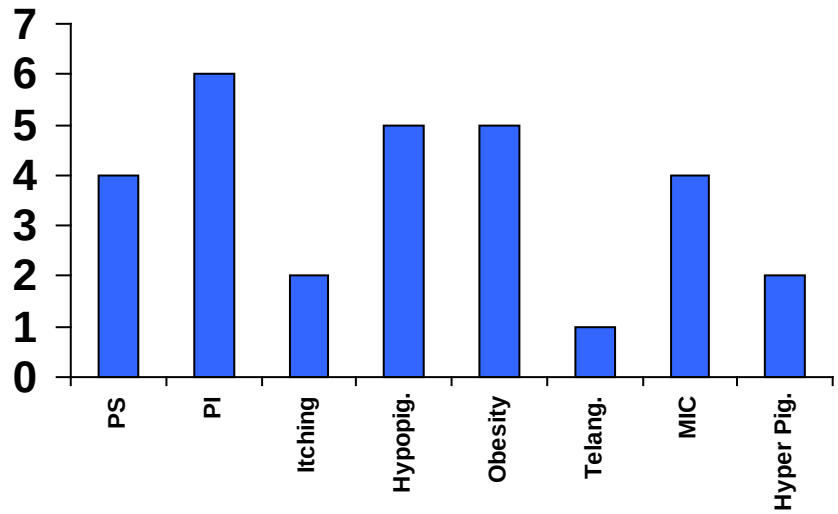


Figure:9



PS=Profuse sweating; PI=Pain at injection site; Hypopig-Hypopigmentation; Telang.-Telangectasia; MIC-Menstrual Irregular Cycles; Hyper Pig.-Hyper Pigmentation

TABLE 7

COMPARING COST OF DRUGS FOR BOTH THE GROUPS

TRIAMCINOLONE AND VERAPAMIL

NAME OF DRUG	COST PER MONTH
TRIAMCINOLONE INJECTION	Rs 55.72 /-
VERAPAMIL INJECTION	Rs.2/

Figure : 10a

Verapamil – Pre Drug Assessment

Subjects : 009 A(Photograph)

Figure : 10 b

Verapamil Post drug Assessment at 18 weeks

Subjects : 009 A(photograph)

Figure: 10c

Verapamil Follow up Assessmentat 52 weeks

Subjects : 009 A(Photograph)

Figure : 11a

Triamcinolone – Pre Drug Assessment

Subjects: 015 B(Photograph)

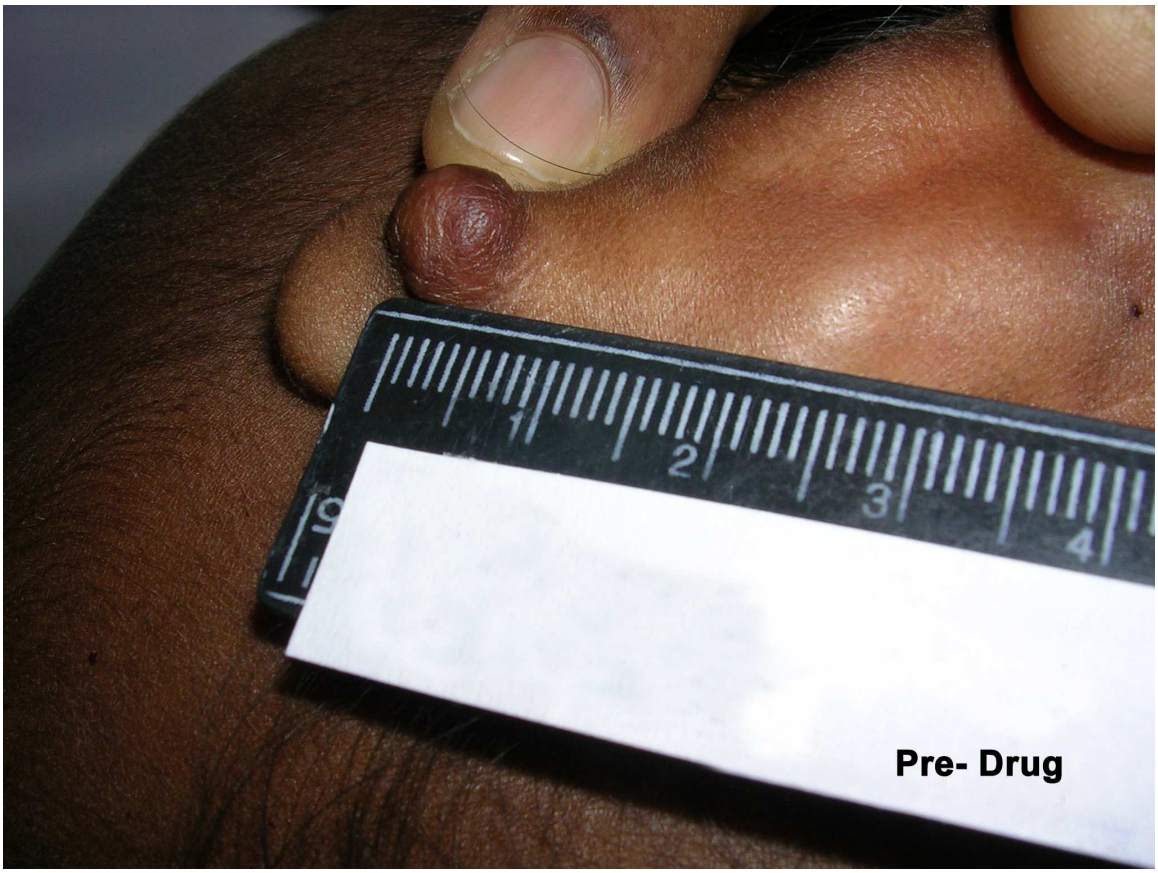


Figure : 11b

Triamcinolone – Post Drug Assessment at 12 weeks

Subjects: 015 B(Photograph)

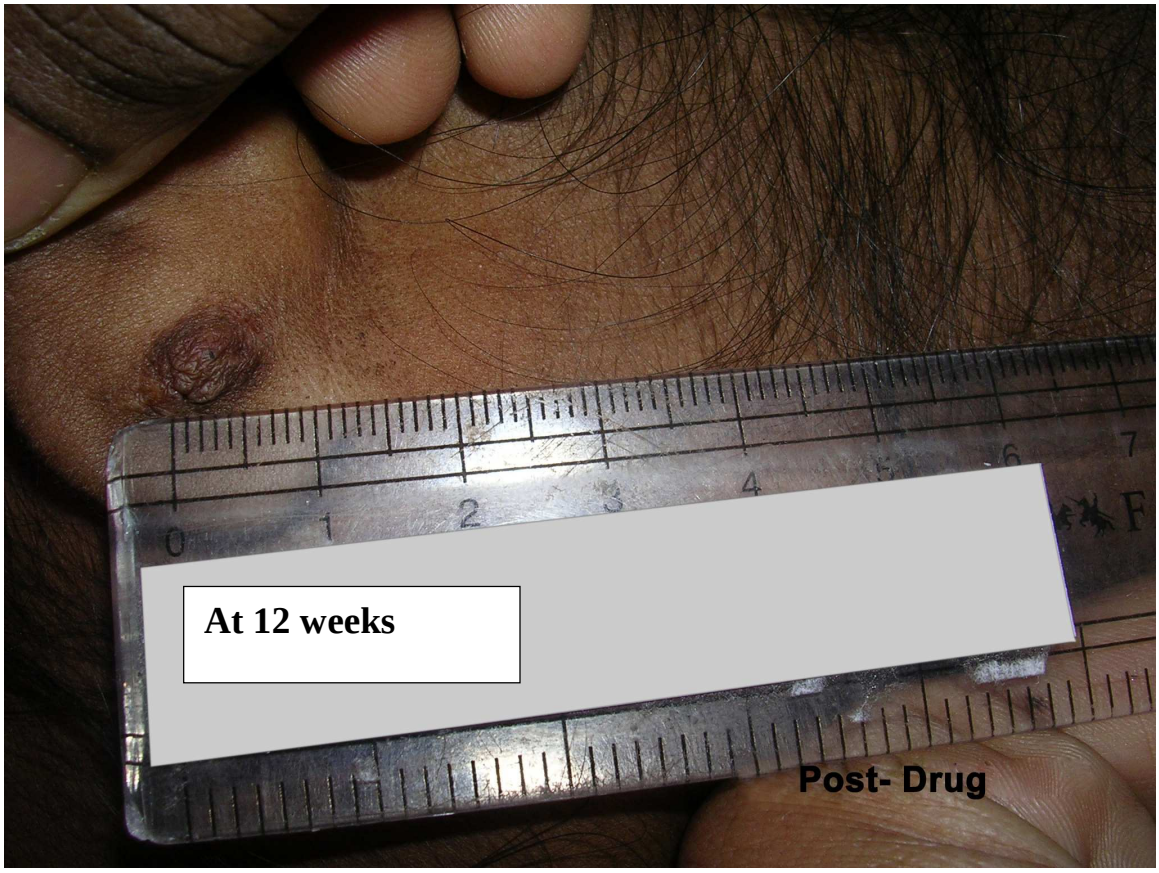
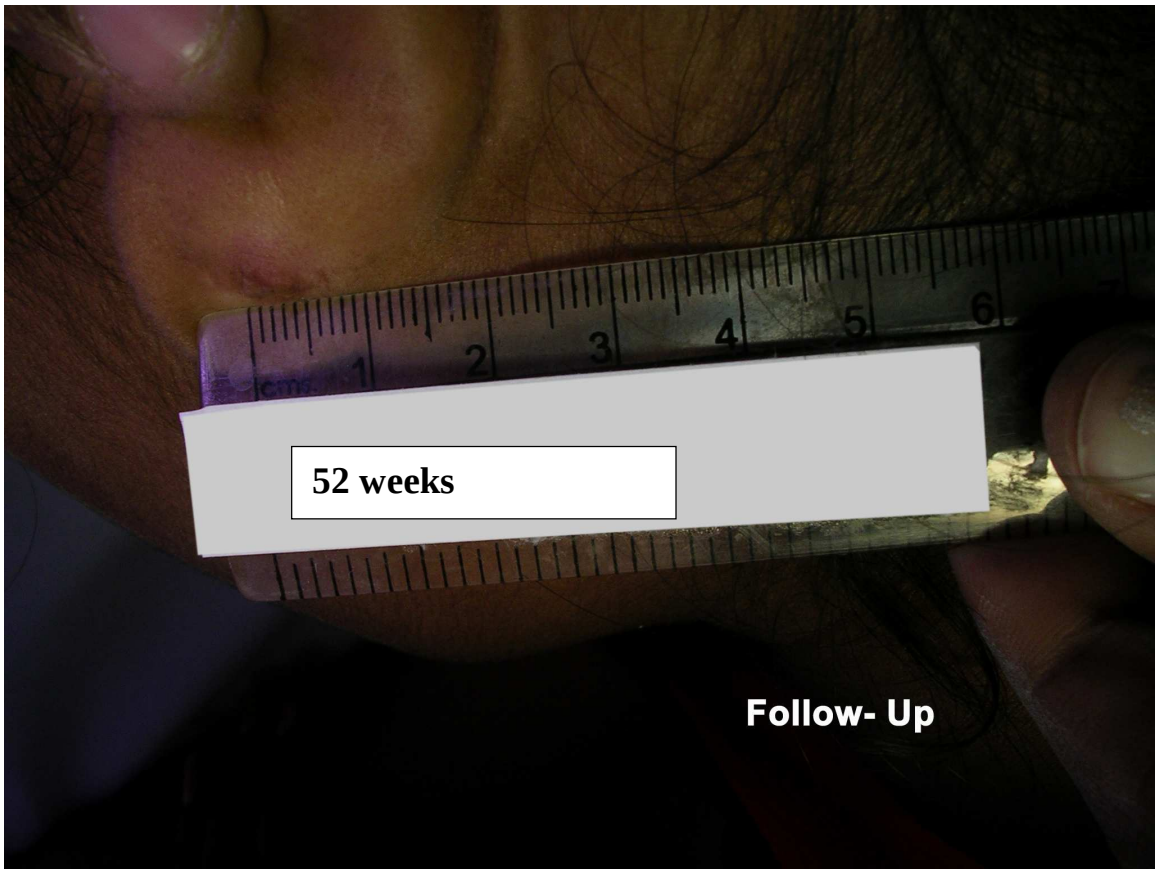


Figure : 11c

Triamcinolone – Follow up Assessment at 52 weeks

Subjects: 015 B(Photograph)



DISCUSSION

Hypertrophic scars and keloids are relatively common and important problems encountered in clinical practice. Inspite of many advances in the understanding of wound healing and scar formation, the treatment of these conditions is still controversial. (Eray .Copcu et al., 2004).

There are several non pharmacological methods of treating hypertrophic scars and keloids but they have drawbacks such as high cost (silicone gel sheeting) , poor efficacy (surgery and laser therapy) , recurrence(surgery) and adverse effects like malignancy (radiation therapy).Pharmacological modes of treatment also have drawbacks such as poor efficacy (tacrolimus) , high cost (bleomycin and interferon) recurrence (5-fluorouracil) and adverse drug reactions (5 – fluorouracil, bleomycin , interferon and triamcinolone).

The prophylaxis of hypertrophic scar and keloid formation is more effective than its subsequent treatment. The prophylaxis involves the application of measures that reduce the risk of the development of problem-causing scars.

The pathogenesis of keloid includes excessive amount of collagen and other extracellular matrix components ,Abergel et al., (1985) showed an abnormal composition and metabolism of collagen in hypertrophic scars and keloids.

Calcium channel blockers were first used in collagen matrix on the connective tissue remodeling by Lee and Ping in 1990. Doong et al., (1996) presented their observation about calcium channel blockers and claimed that they

depolymerize actins filaments and alter the shape of fibroblast cells from bipolar to spherical and that this process results in an increase in procollagenase production.

The first successful results of the intralesional injection of verapamil were presented in 1994 in burns scars (Lee et al.,1994). Lawrence, presented his experience with the intralesional verapamil injection and pressure therapy in the treatment of earlobe scars and reported the cure rate of 50%. Finally, D' Andrea et al., (2002) concluded that the treatment of keloids with perilesional surgical excision and topical silicone followed by an adjuvant treatment with intralesional verapamil hydrochloride injection at certain intervals offered a higher rate of resolution than other therapeutic strategies. For these reasons other modes of pharmacological therapy need to be evaluated.

The present study has compared the efficacy of intralesional verapamil with that of intralesional triamcinolone in the treatment of hypertophic scars and keloids using a randomized, single-blind study design. It was not possible to use a double-blind study design in the present study because triamcinolone is an oily emulsion whereas verapamil is a plain coloured solution.

It was found in the present study that intralesionally administered verapamil and triamcinolone exerted improvement in patients with hypertrophic scars and keloids. Clinical parameters of the scar such as vascularity , pliablility and height (measured using Vancouver scale) and width and height (measured using centimeter scale) showed improvement .The improvement was noted after 3 weeks of treatment with both triamcinolone and verapamil and was present after one year of follow-up

after stopping treatment. Scar pigmentation was not changed desirably by either of the drugs. With triamcinolone, hypopigmentation or hyper pigmentation were noticed in some of the patients . Length of the scars were not altered significantly by both the drugs .

To this investigator's knowledge this is the first randomized controlled study to demonstrate the efficacy of intralesional verapamil in the treatment of hypertophic scars and keloids. There have been other reports showing the efficacy of intralesional verapamil in the treatment of these disorders, but they have been case reports (Lee et al., 1994)or studies that used surgical treatment in conjunction with verapamil(D'Andrea et al., 2002 ; Eray .Copcu et al., 2004). The results of the present study suggest that verapamil is clinically safe for patients with hypertrophic scars and keloids. When compared with other methods of treatment, injection of verapamil appears to be capable of inducing a rapid beneficial effect in the scars.

Verapamil, in addition to being found to be effective in treating hypertrophic scars and keloids in the present study, was also found to be less toxic than triamcinolone, causing a lower incidence of adverse drug reactions (Figure.8 &9). Other advantages of verapamil over triamcinolone include the fact that the cost of verapamil is considerably less than that of triamcinolone and that verapamil (Table7), being a solution, is much easier to inject intralesionally than triamcinolone, which is an oily emulsion and causes severe pain at injection site. Hence verapamil may be a suitable alternative to triamcinolone in the treatment of hypertrophic scars and keloids, especially in the context of developing countries like India.

LIMITATIONS

1. Double blind study could not be performed because triamcinolone is an oily emulsion whereas verapamil is a plain coloured solution.

2. Hypertrophic scars were not distinguished from keloid scars using electron microscopy due to financial constraints. Electron microscopy would have given confirmation of the differences between hypertrophic scars and keloids.

3. Recurrence rate was followed up for only 12 months in the present study due to time constraints. It would have been good to follow up the patients for 3 to 5 years.

SUMMARY AND CONCLUSIONS

This study compared the efficacy of verapamil with that of triamcinolone in treating hypertrophic scars and keloids, both drugs given by injection intralesionally. Triamcinolone is well established to be effective in treating these conditions but is known to have drawbacks like causing pain at the site of injection and causing adverse effects. It was found in the present study that verapamil, like triamcinolone, significantly improved all clinical parameters of the scars that were investigated. The improvement was observed after 3 weeks of treatment and was present one year after follow-up. Patient acceptability of verapamil was also found to be good and the incidence of adverse drug reactions was found to be lower in patients who received verapamil than in those who received triamcinolone. Hence, intralesional verapamil may be a suitable alternative to triamcinolone in the treatment of hypertrophic scars and keloids.

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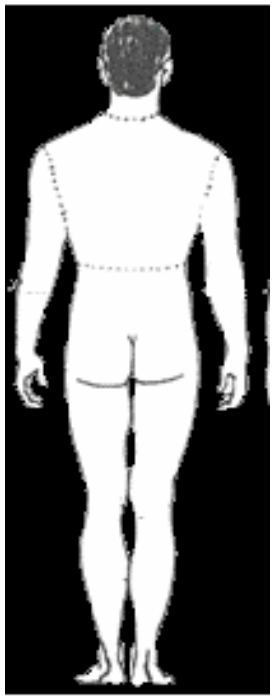
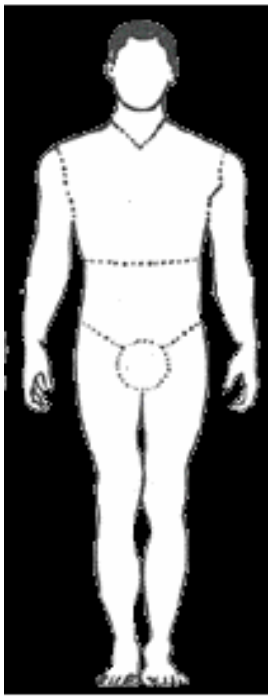
BURN SCAR ASSESSMENT

VANCOUVER SCALE (Mary .Jo.Barzya et al 1995)

PATIENT NAME:



VANCOUVER SCALE



MODIFIED VANCOUVER SCALE

PIGMENTATION (M)
0 - Normal colour that closely resembles to the body
1 - Hypopigmentation
3 - Hyperpigmentation

VASCULARITY (V)
0 – Normal Colour
1 -pink
2 –red
3 –purple

PLIABILITY (P)
0 – Normal
1 – Supple – flexible with minimal resistance
2 - Yielding – giving way to pressure
3 - firm – inflexible
4 - banding – rope – like tissue that blanches with extension of scar
5 - contracture

HEIGHT (H) **Scale in mm**
0 - Normal – flat
1 - < 2mm
2 - < 5mm
3 - > 5mm

PIGMENTATION (M)
0 - Normal colour that closely resembles to the body
1 - Hypopigmentation
3 - Hyperpigmentation

VASCULARITY (V)
0 – Normal Colour
1 – brown
2 –Pink
3 –red

PLIABILITY (P)
0 – Normal
1 – Supple – flexible with minimal resistance
2 - Yielding – giving way to pressure
3 - firm – inflexible
4 - banding – rope – like tissue that blanches with extension of scar
5 - contracture

HEIGHT (H) **Scale in mm**
0 - Normal – flat
1 - < 2mm
2 - < 5mm
3 - > 5mm

TABLE 12:

SCAR - SCALE ASSESSMENT SCORES

FOR VERAPAMIL AND TRIAMCINOLONE